EXPONENT

EXTERNAL MEMORANDUM

TO: Scientific Advisory Board (SAB) Members
Genevieve Matanoski, M.D., Dr.P.H., Chair

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FROM: Joyce Tsuji, Ph.D.

DATE: January 17, 2006

PROJECT: BE02909.001 0401

SUBJECT: Comments on the EPA SAB Report Regarding Inorganic Arsenic

EPA has requested comments and advice from the Science Advisory Board (SAB) regarding EPA's recent hazard characterization for organic arsenic herbicides and on their revised hazard and dose-response assessment/characterization of inorganic arsenic. The SAB released a draft report on December 27, 2005 for public review.

This memorandum provides my comments on this report for EPA and the Science Advisory Board Arsenic Review Panel to consider. These comments focus on two specific issues:

1. The dose-response relationship for inorganic arsenic carcinogenicity
2. The water intake rate for Asian populations in warm climates such as the Southwest Taiwanese population.

## Dose-Response Relationship

The Science Advisory Board (SAB) was asked whether they concurred on the selection of a linear model to estimate cancer risk following the recommendations of NRC (2001) and to discuss their response in light of the highly complex mode of action for inorganic arsenic and its metabolites. Several lines of evidence support a non-linear relationship when extrapolating from high doses to low doses:

1. Epidemiological Data—The results of studies of populations with lower arsenic exposures (e.g., Lewis et al. 1999; Steinmaus et al. 2003; Lamm et al. 2004; Bates et al. 2004) are not consistent with the linear dose-response models derived from studies of populations with high exposures

(e.g., Morales et al. 2000; Ferreccio et al. 2000) (see comments submitted by Pamela Mink). Results from the low exposure studies are consistent with a non-linear or threshold model.

2. Mechanism and Mode of Action for Carcinogenicity—Multiple mechanisms are possible, but as noted by the SAB, none involve direct reactions with DNA, and thus, all plausible mechanisms are associated with sublinear or "threshold" type dose-response relationships between high and low doses. Some of the modes of action of arsenic at low doses also would induce protective effects against arsenic toxicity and carcinogenicity by up-regulating genes and systems related to control of oxidative stress, DNA repair, and increased levels of glutathione (Schoen et al. 2004; Snow et al. 2005).

3. Effect of Nutrition—Additional studies since NRC (2001) have reaffirmed the effect of inadequate nutrition (such as in the arseniasis endemic area of SW Taiwan) in increasing arsenic toxicity. In addition to the evidence within the SW Taiwanese population (Chen et al. 2001), evidence from other impoverished populations (Milton et al. 2004; Mitra et al. 2004; Gamble et al. 2005) and *in vivo* (humans and animals) and *in vitro* studies (Spallholtz et al. 2004; Yang et al. 2002; Miyazaki et al. 2005) likewise indicates that nutritional deficiencies increase susceptibility to arsenical health effects. The effect of nutritional differences may be more dramatic at lower doses in which protective mechanisms may be more effective against arsenic toxicity.

4. Modeling of Dose-Response Data—The dose-response data within the SW Taiwan population in the arsenic endemic region show a sublinear relationship over the high to low dose range (Morales et al. 2000). Linear or supralinear fits are indicated only when the low end of the data is anchored with the use of an external comparison population (see comments submitted by Kenneth Brown).

The SAB's recommendation to use a linear model appears to be based largely on EPA's cancer risk guidelines, which specify that the default assumption is linear extrapolation from the point of departure if the mode of action is not understood, and because in the case of arsenic, multiple modes of action may be operating. This interpretation of EPA's cancer risk guidelines, however, does not consider a weight of evidence approach for a chemical such arsenic for which multiple lines of evidence support a non-linear relationship between high doses and low doses. Thus, the SAB's recommendation to also consider modeling approaches other than a linear relationship is better supported by the scientific weight of evidence than is a linear approach.

## Water Intake Rate

The amount of arsenic-contaminated water ingested is an important parameter in estimating the arsenic dose for the SW Taiwanese population. The SAB was asked to comment on the water intake for the SW Taiwanese population during the time of their exposures in the past. Several factors would increase the amount of water intake for this population over populations in the U.S.

- Their impoverished conditions in the past[1] would result in fluid intake being derived from well water in their village rather than from purchased beverages.
- The warm climate and heavy labor[2] would increase their water intake.
- Their diet of predominantly rice and dried yams would require a considerable amount of water for preparation and cooking.

The SAB draft report notes that information on water intake rates from the SW Taiwanese is available from "a small study by Yang and Blackwell and an EPA informal, anecdotal assessment (as cited in EPA 2005) that include only information on drinking water consumption." The SAB draft report also notes that information from other studies in other Asian populations of low socioeconomic status is available (West Bengal, Chowdhury et al. 2001; Bangladesh, Watanabe et al. 2004). Because the first of these two papers is cited as "Chowdhury et al. 2001 cited in EPA 2005," it appears that the original paper was not available for the SAB's review. The SAB draft report states "These studies report mean daily drinking water intake of 1 to 3.5 L, with an additional 1 L associated with food preparation."

Nevertheless, according to U.S. EPA (2005a,b), the Yang and Blackwell study estimated a range of 1 to 3 L/day of drinking water, not a mean of 1 L/day. Chowdhury et al. (2001) and Watanabe et al. (2004) indicate means of 3 to 4 L/day for adults.

Chowdhury et al. (2001, p. 402-403; see also Table 9):

> The average water intake per day for adult males, adult females, and children is 4 L, 3 L, and 2 L, respectively. Those who work in the field consume more water (average 6 L) and during summer the average water intake for those working the field is as high as 10 L. Villagers also consume arsenic from Pantavat* and water added to food preparations like rice, soup, curry and drinks

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[1] According to Morales et al. (2000), death certificates from 1973 to 1986 were examined. Well water arsenic concentrations were measured in 1964–1966. Artesian wells were closed gradually with the last artesian well closed in 1970. Thus, exposures would be from the 1960s and earlier.

[2] According to U.S. EPA (2005a), interviews in SW Taiwan indicated that most of the population was engaged in relatively heavy labor.

> like tea. After thorough discussions with the villagers, it appears that this is equivalent to the consumption of 1 L of water for an adult and 500 ml for a child.
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> * Rice mixed with water, a common breakfast food.

Watanabe et al. (2004, p. 272):

> Mean water intake obtained by the self-reported method was found to be around 3 L/day with substantial individual variation (the maximum = 6 L/day), no sex difference, and significant between-community difference.

The above intake amounts of Watanabe et al. (2004) refer to direct water intake rather than water consumed from food preparation. Watanabe et al. (2004) also note: "Unless otherwise described, the simple term *water intake* refers to *direct* water intake, and the *indirect* water intake will be described only as *indirect water intake.*"

Thus, the SAB should consider mean drinking water intakes for adults that are around 3 to 4 L/day with an additional 1 L/day from food preparation. Means rather than low-end estimates (e.g., 1 L/day for drinking water) should be considered in the uncertainty analysis because such a low-end estimate would not be sustainable for years of exposure under the conditions of the population in SW Taiwan.

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